REMARKS

Claims 10, 12, 15-18, 41, 42 and 44-80 present appear in this case. No claims have been allowed. The official action of July 10, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to the therapeutic use of an A3-selective adenosine A3 receptor agonist (A3RAg), in an effective amount that assures selectivity, for inhibiting abnormal cell proliferation, including the treatment of cancer, and for inducing G-CSF production or secretion.

The examiner has acknowledged applicant's election of species without traverse. However, regardless of whether or not the election was traversed, if the elected species is found to be allowable then applicant is entitled to examination of the full genus, or at least a reasonable number of additional species.

The examiner further acknowledges applicant's election with traverse of Group XI and has made the restriction requirement final. Claims 1-9, 13, 14, 19 and 22-40 have been withdrawn from further consideration.

All of the claims 1-9, 13, 14, 19 and 22-40 have now been deleted without prejudice toward the continuation of

prosecution thereof in a divisional application, or toward reinserting such claims in this case if a linking claims is found to be allowable.

The examiner's attention is invited to the fact that present claims 10, 12, and 15-18 relate to induction of G-CSF production, while the remaining claims relate to inhibition of abnormal cell growth and/or treatment of tumors. It should be noted that the specification, at page 4, lines 14-29, clarifies that these are two different effects. Induction of G-CSF production counters myelotoxicity but has no direct effect on inhibiting abnormal cell growth. Induction of G-CSF is not the mechanism by which A3RAg inhibits abnormal cell growth. Applicant is pleased that the examiner is willing to examine these claims with the elected embodiment, notwithstanding the fact that they are more appropriately drawn to the invention that the examiner characterized as being Group I. If these claims are found to be allowable, then applicant will request permission to reinsert claims 1-9, 19 and 22-25 in this case as such claims are not patentably distinct from claims 10, 12 and 15-18, which the examiner is examining in this case.

On October 16, 2003, a telephone conference was conducted between the undersigned and Examiner Lewis concerning this issue, at which time Examiner Lewis stated

that claims 10-12, 15 and 18 were considered to be linking claims as they are also included in Groups VI, VII, VIII, XI, XIV, XV and XVI. Accordingly, it is applicant's understanding that, if claims 10-12 and 15-18 are found to be allowable, then applicant will be afforded the opportunity to resubmit claims directed to Groups VI, VII, VIII, XI, XIV, XV and XVI.

Claims 10-12, 15-18, 20, 21 and 41-56 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the treatment of lymphoma, melanoma and colon cancer, does not reasonably provide enablement for treating all forms of abnormal growth for all types of cells or for treating all types of cancer. The examiner states that undue experimentation is required to determine which cells or cancer lines would be affected by an adenosine A3 receptor agonist for which the present invention is applicable and that there is a great deal of unpredictability in the art. The examiner states that the working examples directed to lymphoma, melanoma and colon cancer are not sufficient to support the breadth of the claims. This rejection is respectfully traversed.

While it is true that the specification exemplifies the use of A3RAg for a number of malignancies, the invention disclosed in the specification enables a method for inhibiting abnormal cell proliferation in a subject in general. The

examiner's attention is drawn to page 23, lines 13-15, of the specification where it is stated that:

> The proliferation-inhibiting embodiment is useful for the treatment of a variety of abnormalities associated with the abnormal cell growth such as cancer, psoriasis and some autoimmune diseases.

Furthermore, applicant has subsequently shown (published as well as unpublished data) that the invention may also be applied to other types of cancers, including prostate carcinoma and pancreatic carcinoma. Attached hereto is a Declaration under 37 C.F.R. §1.132 prepared by the inventor, Prof. Pnina Fishman, describing experimental results regarding these types of cancer. The Declaration reports that IB-MECA was shown to inhibit growth and proliferation of prostate carcinoma (results were published in Fishman et al, Anticancer Research 23:2077-2083 (2003), Annex B to the Declaration), as well as pancreatic carcinoma (experiment discussed in paragraph 5 of the Declaration and results shown in Annex C).

A person skilled in the art would know how to apply the teachings in the specification to other types of cancer, as exemplified in the aforementioned Declaration. To begin with, the fact that A3RAgs are effective in diverse hyperproliferating cells, such as melanoma, colon carcinoma and lymphoma, provides a very good basis for predicting that A3RAgs will be broadly effective in treating abnormal cell growth. Furthermore, the additional results reported in the

Declaration provide an additional proof for the justification of the scope of the claims. Moreover, the results in the Declaration also show that the broad application of the invention as defined in the claims does not require undue experimentation: the route of administration and a dose that were effective in the experiments that are exemplified in the specification, are also effective in the additional disease models of prostate carcinoma and pancreatic carcinoma. This shows that the teaching in the specification is widely applicable, contrary to the examiner's opinion. Also, it demonstrates the predictability in the teaching of the invention.

In summary, the additional data and the above arguments show that (i) no undue experimentation is required; (ii) the disclosure in the specification is highly predictive as for the full scope of the claims; and (iii) melanoma, colon carcinoma and lymphoma are very different diseases. The fact that activity was demonstrated in all, as well as in prostate and pancreatic cancers, provides sufficient support for the full breadth of the claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 15, 46 and 53 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite in

referring to a preceding location in the claims, such as "above". The examiner states that such reference is superfluous if the definition or meaning is already set forth in a claim. The examiner recommends that these phrases be deleted from the claims as superfluous.

The claims have now been amended in order to delete the references which the examiner considers to be indefinite, thus obviating this rejection.

Claims 10, 11, 15-18, 20, 41-43 and 46-49 have been rejected under 35 U.S.C. §102(b) as being anticipated by Kohno. The examiner states that Kohno teaches that adenosine A3 receptor agonists, such as IB-MECA and Cl-IB-MECA, induce apoptosis in HL-60 human promyelocytic leukemia cells and, therefore, have therapeutic value in the treatment of leukemia. The examiner states that the induction of G-CSF production would inherently take place because it is known that induction of G-CSF production is of potential therapeutic value in the treatment of leukemia. This rejection is respectfully traversed.

First of all, with respect to the induction of G-CSF production, claim 10 is directed to a method for therapeutic treatment to induce G-CSF production or secretion by administering A3RAg to a "subject in need thereof". As the examiner recognizes, Kohno is totally silent about induction

of G-CSF. While the examiner states that the induction of G-CSF production is of potential therapeutic value in the treatment of leukemia, the examiner supplies no support for this statement. As indicated in the present specification, the induction of G-CSF is a completely different activity of A3RAg than inhibition of growth proliferation. The examiner has cited no reference that would suggest that a person having leukemia is in need of G-CSF production. Accordingly, claims 10, 12 and 15-18 are not anticipated by Kohno.

With respect to the remaining claims, claim 41 has now been amended to be directed to a method for inhibiting abnormal cell proliferation in a subject in need thereof by administering to the subject an amount of an A3-selective adenosine A3 receptor agonist in a manner such that it exerts its prime effect through the adenosine A3 receptor, the amount being effective to selectively inhibit abnormal cell proliferation. Thus, in accordance with the present invention, the A3RAg is administered such that it exerts its effect through the A3 adenosine receptor. See, for example, page 10, line 7, of the present specification. The amount being administered must be effective to selectively inhibit abnormal cell proliferation. See page 6, lines 28-29; page 8, line 2; and page 13, line 15, of the present specification. By definition, such selectivity will occur with a specific and

selective agonist and at a level in which other receptors will essentially not be activated.

In the case of IB-MECA and Cl-IB-MECA, for example, this occurs at in the nanomolar (nM) concentration range - see Examples 2 and 3 which uses 0.01 μM of the adenosine receptor agonist. Like any other agent that specifically interacts with a defined target, an A3RAg, if given at high enough dosages/concentrations, may interact also with other targets such as other adenosine receptors. In this regard, attention is directed to paragraph 8 of the attached Fishman Declaration. This establishes, for example, that IB-MECA (an A3RAg) has a binding affinity (K_i) of 0.47 nM to the A_3 adenosine receptor and a much higher K_i to the 3 other adenosine receptors: 560 nM to the A_{2A}, larger than 1000 nM to the A_1 and 42,300 nM to A_{2B} adenosine receptor (see paragraph 8 of the Declaration). Thus, although IB-MECA has a selectivity of more than 3 orders of magnitude for binding to the A_3 adenosine receptor, if the concentration/dosage is sufficiently increased, other adenosine receptors may be activated as well. The present claims require that the A3RAg be administered in a manner and amount such that activation of the other receptors will be avoided, i.e., that it be A3-selective. The agents mentioned in Kohno are A3RAgs that are given at a very high concentration, in which case they act

through different mechanisms (see below) and thus do not induce their action primarily through the A3 adenosine receptor.

Kohno, on the other hand, uses concentrations which are 3 orders of magnitude higher to obtain the desired effect (the A3RAg, Cl-IB-MECA, is applied at a μM concentration range - see bottom of page 905: 10-60 μM). At such concentrations, A3RAg induces apoptosis in all types of cells, normal as well as tumor cells. See the attached Fishman Declaration at paragraph 8, as well as Kim et al (Annex E of the Declaration), page 877, left column, first two lines of the Discussion. Thus, Kohno teaches that high concentrations of A3RAg cause apoptosis, but only showed it on tumor cells, and was silent about occurrence in non-cancer cells. Therefore, Kohno does not teach selective inhibition of tumor cells. Furthermore, from Kim it can be deduced that the effect seen in Kohno is not primarily mediated through the A3 adenosine receptor. The present invention, on the other hand, teaches inhibition of proliferation (rather than apoptosis) of cancer cells using an agonist that specifically interacts with the A3 adenosine receptor; for the prime effect to be mediated through the A3 adenosine receptor, the level of administration is invariably such so as not to activate other adenosine receptors.

The *in vivo* data presented in the specification as well the Fishman Declaration (see paragraph 13) shows a potent effect at doses of the A3RAg which yield plasma levels of the agonist which are high enough to activate the A3 adenosine receptor but not sufficiently high to activate any other adenosine receptor.

Claim 50 relates to a combined treatment of an A3RAg and chemotherapy but overall has the same limitations as claim 41. New independent claim 57 specifically states that the effect of inhibiting proliferation of abnormal cells is achieved with an A3RAg without activating adenosine receptors other than the A3 adenosine receptor. New independent claim 79 is directed to a specific dose of below 100 μg/Kg. None of these claims is anticipated by the prior art.

Accordingly, none of the present claims are anticipated by Kohno. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 10, 11, 15, 16, 20, 41-43, 46 and 47 have been rejected under 35 U.S.C. §102(b) as being anticipated by Mittelman. The examiner states that Mittelman teaches that N^6-(benzyladenosine) is a potent cytokinin and active in the mouse leukemia system. The examiner considers that G-CSF production is inherent to the disclosed compound. This rejection is respectfully traversed.

Mittelman describes clinical studies that were carried out with N^6-(Δ^2-isopentenyl) adenosine (IPA) and N^6-benzyladenosine in which the anti-cancer effects of these adenosine derivatives was tested in cancer patients. These compounds are not specific A3 adenosine receptor agonists (see also paragraph 14 of the Fishman Declaration). As all of the claims require the use of A3-specific adenosine A3 receptor agonists, none of the claims are anticipated by Mittelman. Reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 10-12, 15-18, 20, 21 and 41-49 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kohno in view of Jacobson. The examiner states that Jacobson teaches various adenosine A3 receptor agonists for indications other than those of the present claims. The examiner considers it to have been obvious to administer the A3RAg of Kohno orally as Jacobson teaches that such compounds are easily formulated for oral administration. The examiner also considers it obvious to use an A3RAg in combination with one or more other chemotherapeutic agents. This rejection is respectfully traversed.

Jacobson does not supply any of the deficiencies of Kohno as discussed above. Therefore, no combination of Kohno with Jacobson can render obvious any of the present

independent claims. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 10-12, 15-18, 20, 21 and 41-56 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kohno and an International Publication of Can-Fite in view of Jacobson. The examiner states that Can-Fite teaches that adenosine has an effect in inducing proliferation of bone marrow cells, resulting in an increase in the number of leukocytes, and particularly of neutrophils in the peripheral blood, thereby exhibiting a protective effect against some toxic effects of chemotherapeutic drugs. Thus, the examiner considers it obvious that the A3RAg of Kohno could also induce proliferation of bone marrow cells, thereby exhibiting a protective effect against some toxic effects of chemotherapeutic drugs. This rejection is respectfully traversed.

As the examiner notes, Can-Fite is directed to the administration of adenosine. However, adenosine has a very low affinity for A3 receptors, approximately two orders of magnitude below its affinity for the A1 and A2 receptors. Therefore, the teachings of Can-Fite do not render obvious anything in the present invention in which the A3RAg is A3 selective and exerts its prime effect through the A3 receptor. In any event, neither Can-Fite nor Jacobson add anything to

the deficiencies of Kohno as discussed above. Therefore, the dependent claims are allowable for the same reasons that the independent claims are not anticipated by Kohno, as discussed above. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

It should be noted that, at page 15, lines 9-10, of the specification as originally filed, many compounds and their synthesis procedures were incorporated by reference to a number of patents and patent publications. The present specification now adds explicit reference to many of these compounds. As this amendment merely states explicitly that which had previously incorporated been by reference only, no new matter is being inserted by means of this amendment.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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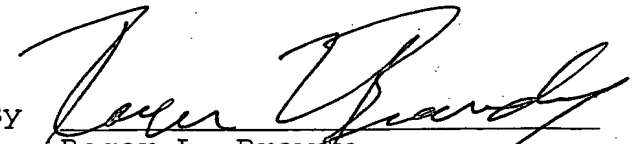
By 
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